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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,057	VON KNEBEL DOEBERITZ ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 15, 2007, has been entered.

1. The amendment filed February 15, 2007, is acknowledged and has been entered. Claims 7-18 have been canceled. Claim 1 has been amended. Claims 19-24 have been added.

2. Claims 1-6 and 19-24 are pending in the application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Terminal Disclaimer

4. The terminal disclaimer filed on February 15, 2007, disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration dates of any patents granted on Applications Nos. 10/633,484 and 10/569,758, has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Amendment

5. The amendment filed on February 15, 2007, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment[1], Applicant is advised to correct the following deficiency in replying to this Office action:

(a) The amendment to the claims is non-compliant because the status identifier of claim 1, which appears in parentheses, does not properly indicate that claim 1 has been amended.

Briefly, the amended amendment practice requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled", "withdrawn", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., ~~strikethrough~~); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). The text of "canceled" and "not entered" claims must not be presented; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

(b) The amendment to the specification is non-compliant because it replaces two paragraphs at page 3, beginning in line 24, without showing the changes that have been made relative the immediate prior versions of those paragraphs.

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[1] See M.P.E.P. § 714.03.

Again, as explained previously, 37 CFR § 1.121 provides for amendments to the specification that are limited to the substitution of existing paragraphs by amended versions thereof, provided that the changes that have been made relative to their immediate prior versions are marked in the prescribed manner, the insertion of new paragraphs, and the deletion of entire paragraphs from the disclosure. Not provided for by the rule are amendments to the specification made by deleting an entire paragraph, only to replace it with an amended version without showing how the original version of the paragraph has been changed.

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the specification" section of applicant's amendment must be re-submitted. 37 CFR § 1.121(h).

6. The amendment filed February 15, 2007, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is the recitation at page 8, in the paragraph beginning in line 4, of "Tween™" as an example of a non-ionic detergent. The original specification only provides written support for Tween™-20, a species of the genus of the exemplary non-ionic detergent.

Applicant is required to cancel the new matter in the reply to this Office Action.

7. Applicant's remarks beginning at page 10 of the amendment filed February 15, 2007, are acknowledged, but without acquiescence to any statements or implications thereof.

Priority

8. Applicant has amended the statement of continuity at the first page of the specification to strike the reference of the instant application as a continuation-in-part of prior filed Application No. 09/743,103.

As noted in the preceding Office action mailed August 16, 2006, the effective filing date of present claims 1-3, 5, and 6 is deemed the filing date of U.S. Patent Application No. 10/633,484, namely July 31, 2003; whereas the effective filing date of claim 4 is the filing date of the instant application (i.e., August 26, 2003).

The effective filing date of newly added claims 19-24 is the filing date of U.S. Patent Application No. 10/633,484, namely July 31, 2003.

Specification

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks appearing in the specification include Heraeus™ (see, e.g., page 26, line 21) and Biofuge™ (see, e.g., page 26, line 25).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claim 19 is directed to the method of claim 1, wherein the lysis buffer comprises at least one composition of a recited group including "alkaline compositions".

Notably the language of claim 19 finds written support in original claim 10.

The as-filed specification, however, does not provide antecedent basis for this claim language because it merely discloses the body samples may be solubilized in any suitable solvent such an aqueous solution of alkali hydroxides such as, e.g., NaOH or KOH (paragraph [0030] of the published application). This disclosure does not provide proper antecedent basis for a claim that is directed to a solubilization or lysis buffer comprising any "alkaline composition".

Grounds of Rejection Withdrawn

11. Unless specifically reiterated below, Applicant's amendment and/or arguments filed February 15, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed January 25, 2007.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

12. The rejection of claims 1, 3-6, 23, and 24 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671), is maintained, as evidenced by U.S. Patent No. 6,403,383 B1.

At page 8 of the amendment filed February 15, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Von Knebel Doeberitz et al. does not teach solubilizing the cervical body sample in a lysis buffer and reacting the solubilized sample in the lysis buffer with an antibody that binds p16, so as to detect the overexpression of p16 in the solubilized sample.

The Examiner disagrees.

At column 2, lines 41-58, Von Knebel Doeberitz et al. discloses the following:

> The (over)expression of cell cycle regulatory proteins can be detected on a nucleic acid level or protein level. Regarding the detection on a protein level, it is possible to use, e.g.,

> antibodies which are directed against cell cycle regulatory proteins. These antibodies can be used in various methods **such as Western blot, ELISA or immunoprecipitation** [emphasis added]. It may be favorable for the antibodies to be fixed on solid carriers such as test strips or latex particles.

As explained in the preceding Office action, although Von Knebel Doeberitz et al. does not expressly teach the process by which the overexpression of p16 is determined comprises lysing the cells and solubilizing the protein, Von Knebel Doeberitz et al. teaches the determination is made by, e.g., Western blot analysis, a process briefly described by Example 2 at column 4, lines 55-67, *which involves the preparation of cell extracts*. As also explained previously, the disclosure of Geradts et al. evidences that fact that the determination of the overexpression, which is made by Western blot, comprises the step of lysing the cells and solubilizing the protein to be detected; see entire document (i.e., the preparation of cell extracts), particularly page 1666, column 2.

As amended the claims are presently amended, however, it is submitted that a process comprising a determination of the overexpression of p16 by a conventional Western blot analysis would be excluded. The claims recite the step of reacting the solubilized sample in the lysis buffer with the antibody, whereas conventional Western blot analysis would typically be performed by electrophoretically separating the proteins in the solubilized sample, transferring the proteins to a blot, and then contacting the affixed proteins with the antibody. Therefore, the claims are directed to immunoassays such as ELISA and an immunoprecipitation assay, in which the solubilized sample in the lysis buffer is contacted directly with the antibody.

So, since Von Knebel Doeberitz et al. explicitly teaches that the step of determining the overexpression of p16 in the sample is performed using either an ELISA or an immunoprecipation assay, the limitations of the claims are met by the disclosure of the prior art.

Newly added claim 23 is specifically directed to the method of claim 1, wherein the overexpression of p16 in the sample is determined using an ELISA.

With regard to newly added claim 24, which is directed to the method of claim 1, wherein the overexpression is determined by a lateral flow assay, as noted above, Von Knebel Doeberitz et al. explicitly teaches that the step of determining the

overexpression of p16 in the sample is performed using an immunoassay in which the antibodies are affixed to solid carriers such as test strips. As evidenced by U.S. Patent No. 6,403,383 B1, the dispersal of the sample after application to such a test strip occurs by a lateral flow or capillary migration of the solution through the test strip[2].

Claim Rejections - 35 USC § 103

13. The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,709,832 B1, as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671), in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

Beginning at page 8 of the amendment filed February 15, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Ryder et al. discloses only certain information, without teaching or suggesting the claimed process.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

14. The rejection of claims 1, 3-6, and 23 under 35 U.S.C. 103(a), as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA*. 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[3] (instruction manual provided with a Bradford

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[2] See column 9, lines 8-16, which disclose the following: "Generally, a test sample is applied to a testing device which may be an immunoassay test strip and the presence of the analyte is indicated by a visually detectable signal such as a color-forming reaction. The test strip is usually of a porous material to which is bound an antigen-specific antibody. In the performance of an assay or test the test solution will be placed in contact with the test strip and there will be a lateral flow or capillary migration of the solution up through the test strip."

[3] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

assay kit manufactured by Bio-Rad) and the American Type Culture Collection™ (ATCC) catalog[4], in view Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant), is maintained.

Beginning at page 9 of the amendment filed February 15, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Khleif et al. does not teach determining the overexpression of p16 in a human cervical body sample by comparing the expression level of p16 within the sample to the expression level present in a healthy human cervical body sample.

Indeed the rejection succinctly identifies this deficiency of Khleif et al., but explains, nevertheless, that Klaes et al. teaches comparing the body sample to be examined with a corresponding body sample which originates from a healthy person; moreover, Klaes et al. teaches the level of p16 in the healthy human cervical body sample is determined from a representative number of healthy human cervical samples; see, e.g., page 279, Table 1.

Therefore, given the combination of the teachings of the cited references, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to practice the method for detecting cervical carcinoma cells according to the method described by Khleif et al. but determining the overexpression of p16 in a human cervical body sample (i.e., a cervical body sample selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations) by comparing the expression level of cyclin-dependent kinase inhibitor p16 within the sample acquired from the subject to the expression levels present in representative number of human cervical body samples originating from healthy persons.

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[4] See http://www.atcc.com/catalog/numSearch/numResults.cfm?atccNum=CCL-2.

Applicant has argued that Khleif et al. does not teach a cervical body sample acquired from a human.

In response, Applicant is again reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, as noted in the preceding Office actions, Khleif et al. does indeed teach a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells); and while Khleif et al. does not however teach acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations, as explained in the preceding Office actions, Klaes et al. teaches acquiring cervical body samples selected from cytological smears, histological specimens, cervical swabs, biopsies, preserved cytological specimens, fixed cell or fixed tissue preparations; see, e.g., page 277, columns 1 and 2.

Applicant has argued that Khleif et al. does not teach or suggest reacting the solubilized sample in the lysis buffer with an antibody that binds p16.

Indeed, Khleif et al. teaches determination of the expression of p16 by Western blot analysis. As explained above, conventional Western blot analysis is typically be performed by electrophoretically separating the proteins in the solubilized sample, transferring the proteins to a blot, and then contacting the affixed proteins with the antibody. Therefore, since the claims now recite the step of reacting the solubilized sample in the lysis buffer with the antibody, the present claims encompass only processes by which the determination of overexpression is made using immunoassays such as ELISA and an immunoprecipitation assay, in which the solubilized sample in the lysis buffer is contacted directly with the antibody[5]. Nonetheless, given the knowledge of the ordinarily skilled artisan at the time the invention was made,

processes for determining the level of expression of p16 in the sample, which utilize such other immunoassays (e.g., ELISA and immunoprecipitation assays[6]) in which the solubilized sample in the lysis buffer is contacted directly with the antibody, are *obvious variations* of the process that is disclosed by the prior art, which would need not be expressly taught by either of the cited references to render the invention unpatentable under 35 U.S.C. § 103(a) over those references.

15. The rejection of claim 2 under 35 U.S.C. 103(a), as being unpatentable over Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 April; **93**:4350-4354) in view of Klaes et al. *(Int. J. Cancer.* 2001; 92: 276-284) (of record; cited by Applicant), as applied to claims 1 and 3-6 above, and further in view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

At page 10 of the amendment filed February 15, 2007 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that Ryder et al. discloses only certain information, without teaching or suggesting the claimed process.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

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[5] Notably, Klaes et al. teaches the determination of the expression of p16 using immunocytochemistry and Western blot assay.

[6] For clarity, claim 24, which is drawn to the method of claim 1, wherein the overexpression of p16 in the sample is determined using a lateral flow assay, has not been included in the rejection because, whereas it would be immediately obvious to choose to use Western blot analyses, ELISAs, and immunoprecipitation assays, it is believed that it would not be so obvious to choose to use, for example, a test strip-based immunoassay, which is a form of a lateral flow assay, without some express suggestion by the prior art to do so. Whereas Western immunoblot assays, ELISAs, and immunoprecipitation assays had been established as routine and conventional, the utility and relative ease of use of lateral flow assays (e.g., test strip-based immunoassays) was, at the time of the invention, continuing to develop.

Double Patenting

16. The rejection of claims 1, 3-6, and 23 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[7] (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad), is maintained.

Beginning at page 11 of the amendment filed February 15, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the invention of claims 1 and 3-6 represent an improved process, not an obvious variant of the processes of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1.

In response, the Examiner disagrees; and although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

As explained in the preceding Office action, claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 are drawn to a method for detecting cervical carcinomas, cervical intraepithelial neoplasias, or cervical carcinomas *in situ*, said method comprising determining the overexpression of cyclin dependent kinase inhibitor p16 in a human cervical body sample selected from a smear, a organ punctuate, and a biopsy by comparing the expression level of the protein within the sample to the expression level of the protein present in a healthy human cervical body sample. According to claims 5, in particular, the overexpression of p16 is determined by detecting the protein in the sample by a process comprising reacting an antibody directed against the protein with the protein in the sample.

In contrast to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1, the instant claims are directed to detecting cervical carcinomas, cervical intraepithelial neoplasias,

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[7] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

or cervical carcinomas *in situ* by a process comprising solubilizing the cervical body sample in a lysis buffer and then determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

Khleif et al. teaches a process comprising obtaining a cervical body sample from a human subject (i.e., cervical cancer cells supplied by the American Type Culture Collection, such as HeLa cells), lysing the cells in a lysis buffer, clearing the lysates by centrifugation, and determining the overexpression of the thus solubilized $p16^{INK4a}$ in the prepared samples; see entire document (e.g., the abstract; page 4350, column 2; page 4351, column 1 and Figure 1; and page 4343, column 1).

As evidenced by Bio-Rad Protein Assay, the protein must be solublized before a determination of the concentration of the protein may be made; see entire document, particularly page 11, item #6.

Accordingly, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have practiced the method according to claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 by solubilizing the cervical body sample in a lysis buffer before determining the overexpression of p16 in a human cervical body sample by comparing the expression level of cyclin-dependent kinase inhibitor p16 within said sample to the expression level present in a healthy human cervical body sample.

Still, claim 1 has been amended to recite the step of reacting the solubilized sample in the lysis buffer with the antibody, and Applicant has argued it would not have been obvious to determine the overexpression of p16 in the sample using the assay taught by Khleif et al. (i.e., a Western immunoblot assay).

As explained above, conventional Western blot analysis is typically be performed by electrophoretically separating the proteins in the solubilized sample, transferring the proteins to a blot, and then contacting the affixed proteins with the antibody. Therefore, since the claims now recite the step of reacting the solubilized sample in the lysis buffer with the antibody, the present claims encompass only processes by which the determination of overexpression is made using immunoassays such as ELISA and an

immunoprecipitation assay, in which the solubilized sample in the lysis buffer is contacted directly with the antibody.

Nonetheless, given the knowledge of the ordinarily skilled artisan at the time the invention was made, processes for determining the level of expression of p16 in the sample, which utilize such other immunoassays (e.g., ELISA and immunoprecipitation assays[8]) in which the solubilized sample in the lysis buffer is contacted directly with the antibody, are *obvious variations* of the process that is claimed by the patent in view of the cited prior art, which would need not be expressly taught by either the claims or the cited prior art to render the invention unpatentable on the ground of nonstatutory obviousness-type double patenting over that combination.

17. The rejection of claim 2 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over U.S. Patent No. 6,709,832 B1 in view of Khleif et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Apr; **93**: 4350-4354), as evidenced by Bio-Rad Protein Assay[9] (instruction manual provided with a Bradford assay kit manufactured by Bio-Rad), as applied to claims 1, 2, 4, and 5 above, in further view of Ryder et al. (*Clin. Chem.* 1988 Dec; **34** (12): 2513-2516), is maintained.

At page 12 of the amendment filed February 15, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that the invention of claim 2 is not an obvious variant of the processes of claims 1, 2, 4, and 5 of U.S. Patent No. 6,709,832 B1 for the same reasons that claims 1, 2, 4, and 5 would not be obvious.

In response, the Examiner disagrees; and although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the preceding Office actions.

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[8] See Footnote #6.

New Grounds of Rejection

Claim Rejections – 35 USC § 103

18. Claims 1 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,709,832 B1 (of record), as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671) (of record), in view of U.S. Patent No. 5,889,169 A, as evidenced by WO 92/20796.

Claims 1 and 19-21 are directed to the method of claim 1, wherein the lysis buffer comprises an anionic and a non-ionic detergent (claims 19 and 20), and further comprises a proteinase inhibitor (claim 21).

As evidenced by Geradts et al., U.S. Patent No. 6,709,832 B1 (Von Knebel Doeberitz et al.) teaches that which is set forth in the above rejection of claims 1, 3-6, 23, and 24 under 35 U.S.C. 102(e).

However, Von Knebel Doeberitz et al. does not explicitly teach lysing the cells in the cervical body sample in a lysis buffer comprises a non-ionic detergent, anionic detergent and/or proteinase inhibitor.

As evidenced by WO 92/20796, U.S. Patent No. 5,889,169 A (Beach et al.) teaches lysing the cells in a sample in a lysis buffer comprises a non-ionic detergent (i.e., Nonidet P-40, or *NP-40*), an anionic detergent (i.e., sodium deoxycholate), and a proteinase inhibitor (i.e., PMSF), so as to determine the level of expression of p16 in the cells using an immunoassay; see entire document (e.g., column 28, lines 42-49). See WO 92/20796 at page 39, lines 16-19.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to practice the process disclosed by Von Knebel Doeberitz et al. by lysing the cells in the cervical body sample in a lysis buffer comprising a non-ionic detergent (e.g., NP-40), an anionic detergent (e.g., sodium deoxycholate), and a proteinase inhibitor (e.g., PMSF) because Beach et al. teaches a lysis buffer comprising NP-40, sodium deoxycholate, and PMSF is suitable for the analysis of the level of p16 in samples of cells by immunoassay. One ordinarily skilled in the art would have been

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[9] See http://www.fhcrc.org/science/labs/hahn/methods/biochem_meth/biorad_assay.pdf

motivated at the time the invention was made to do so to practice the process disclosed by Von Knebel Doeberitz et al.

19. Claims 1 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,709,832 B1 (of record), as evidenced by Geradts et al. (*Am. J. Pathol.* 1999 Jun; **154** (6): 1665-1671) (of record), in view of Ikeda et al. (*J. Histochem. Cytochem.* 1998; **46** (3): 397-403).

Claims 1 and 19-22 are directed to the method of claim 1, wherein the lysis buffer comprises an anionic and a non-ionic detergent (claims 19 and 20), and further comprises a proteinase inhibitor (claim 21), and wherein the anionic detergent of claim 20 is SDS.

As evidenced by Geradts et al., U.S. Patent No. 6,709,832 B1 (Von Knebel Doeberitz et al.) teaches that which is set forth in the above rejection of claims 1, 3-6, 23, and 24 under 35 U.S.C. 102(e).

However, Von Knebel Doeberitz et al. does not explicitly teach lysing the cells in the cervical body sample in a lysis buffer comprises a non-ionic detergent, anionic detergent and/or proteinase inhibitor.

Ikeda et al. teaches solubilizing the cells in a sample of tissue in a lysis buffer comprises a non-ionic detergent (i.e., Triton X-100), anionic detergents (i.e., sodium deoxycholate and SDS), and proteinase inhibitors (i.e., phenylmethylsulfonyl fluoride (PMSF), aprotinin, and leupeptin), so as to determine the level of expression of a protein in the sample using an immunoassay; see entire document (e.g., the paragraph bridging pages 398 and 399).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to practice the process disclosed by Von Knebel Doeberitz et al. by lysing the cells in the cervical body sample in a lysis buffer comprising a non-ionic detergent (e.g., Triton X-100), SDS and/or other anionic detergents (e.g., sodium deoxycholate), and one or more proteinase inhibitors (e.g., phenylmethylsulfonyl fluoride (PMSF), aprotinin, and leupeptin) because Ikeda et al. teaches a lysis buffer comprising Triton X-100, SDS, sodium deoxycholate, and one or more proteinase

inhibitors is suitable for the analysis of the level of proteins in samples by immunoassay. One ordinarily skilled in the art would have been motivated at the time the invention was made to do so to practice the process disclosed by Von Knebel Doeberitz et al.

Conclusion

20. No claim is allowed.

21. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Dai et al., Suneja et al., Castellano et al., Plath et al., and Gump et al. each teach different lysis buffers that are used in processes for measuring the levels of p16 and/or other proteins by immunoassay.

Other art cited, which is pertinent to Applicant's disclosure, includes Wentzensen et al. and Mao et al., both of which teach an evaluation of p16 expression using an ELISA.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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